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Cardiac Performance in Turner's Syndrome Patients on Growth Hormone Therapy

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Key Words
Turner's syndrome · Growth hormone · Heart · Echocardiography

Abstract
Objectives: To investigate possible cardiac morphofunctional alterations observed in 26 Turner's syndrome (TS) patients on prolonged high-dose growth hormone (GH) therapy. ***Study Design:*** We examined 26 TS subjects treated with rhGH (1 U/kg/week) for a mean period of 4.9 years (range 1–7.8) and 37 age-, weight- and height-matched healthy girls. Left ventricular volume, mass, systolic function, cardiac index, systemic vascular resistance and diastolic function were evaluated by two-dimensional and Doppler echocardiography. ***Results:*** Heart rate and systolic blood pressure (BP) were higher in TS patients than in controls, while diastolic BP was lower. Left ventricular volumes, ejection fraction, mass index, M/V ratio and cardiac index did not differ significantly; systemic vascular resistance was slightly decreased. Left ventricular fractional shortening and mean velocity of circumferential shortening were slightly increased while end-systolic meridional stress was decreased in TS. Contractile state was normal in TS. Diastolic function assessment showed a shortening of isovolumetric relaxation and diastolic filling times with an increased atrial contribution and a normal pulmonary venous flow. ***Conclusion:*** Cardiac morphology in TS patients on GH therapy is similar to controls. The observed changes in left ventricular systolic and diastolic function should be interpreted as an adaptation to the higher heart rate and reduced peripheral vascular resistance induced by GH therapy.

Introduction

Growth hormone (GH) therapy is a well-established tool to improve growth and increase final height in children with Turner's syndrome (TS) [1–3]. Since the dose of GH used for TS is higher than that used in GH-deficient (GHD) children, concerns have been raised on the possible cardiovascular side effects associated with this therapy. Left ventricular (LV) hypertrophy, together with increased morbidity and mortality from cardiovascular diseases, are well-known complications of GH excess in acromegalic patients [4, 5]. Furthermore, we also found that GHD children treated for many years with high doses of GH show subclinical morphofunctional alterations of the left ventricle [6]. Since previous studies in TS patients were more focused on the effects of GH treatment on cardiac morphology [7–9], we decided to further explore this field by evaluating heart function, as well as morphology, in TS patients treated with high-dose GH for a mean period of 4.9 years.

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Patients

We evaluated 26 children with TS, selected from a large database of 73 patients not affected by congenital heart defects, who received rhGH (1 U/kg/week) given subcutaneously 6–7 times a week, for a mean period of 4.9 years (1.0–7.8). At the beginning of treatment, chronological age was 8.9 ± 2.8 years, bone age 7.6 ± 3.0 years [10], height standard deviation score (SDS) –2.5 ± 0.7 [11] and BMI SDS 0.4 ± 1.8 [12]. The clinical data of patients and controls at the time of investigation are reported in table 1. Chromosomal analysis demonstrated a 45,X karyotype in 38% of subjects, structural abnormalities of the X chromosome in 15% and mosaicism in 47%. All were prepubertal when treatment was started while, at the time of cardiac evaluation, 9 were still prepubertal and 17 had entered puberty (7 spontaneously, 10 with estrogens). Four patients had Hashimoto's thyroiditis but were euthyroid at the time of investigation, while taking *L*-thyroxine. None had comorbid diseases. Patients had a regular auxological follow-up every 6 months and, once a year, they underwent an oral glucose tolerance test and evaluation of thyroid hormone and TSH levels, with results which were always in the normal range. Thirty-seven healthy girls, which had previously been evaluated in our department for below-average height and who were found to be healthy except for constitutional growth delay, were used as a control group. They were selected from a database of 253 normal subjects and were matched for age, height, weight and body surface area (BSA) (table 1). An age-matched group of untreated TS patients is not available at our institution for ethical reasons as the therapeutic effect of GH in TS has been incontrovertibly established in the literature [1–3]. Informed consent was obtained from all patients and controls.

Table 1. Characteristics of patients and controls (mean ± SD)

	Patients	Controls	p
Subjects	26	37	
Age, years	13.8 ± 2.6	13.6 ± 4.3	NS
Bone age, years	11.9 ± 2.9	11.3 ± 2.6	NS
BMI SDS	–0.9 ± 1.3	–1.2 ± 1.5	NS
Height SDS	–1.7 ± 0.8	–1.6 ± 1.0	NS
BSA, m^2	1.30 ± 0.2	1.24 ± 0.31	NS
HR, beats/min	91.2 ± 12.2	82.4 ± 15.2	<0.05
SBP, mm Hg	116.5 ± 10.7	107.9 ± 9.5	<0.05
DBP, mm Hg	65.2 ± 8.6	69.8 ± 7.4	<0.05
MBP, mm Hg	82.3 ± 8.3	82.5 ± 7.2	NS

HR = Heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure.

Methods

Ultrasound Protocol

All examinations included a complete two-dimensional anatomical study, from subcostal, apical, parasternal and suprasternal notch views, in order to exclude any cardiac anomaly, in particular coarctation of the aorta. Having ascertained the two-dimensional circular short axis configuration of the left ventricle throughout the cardiac cycle, we derived the M-mode tracing of this chamber at the level of central body to obtain systolic and diastolic measurements of the interventricular septum and LV posterior wall thickness and of the LV cavity [13]. PW-Doppler sampling of the mitral inflow was obtained in apical four-chamber view, with the sample volume positioned at the tips of the mitral valve leaflets and sampling of the pulmonary venous flow from the right superior pulmonary vein orifice. Peak systolic and diastolic BP was monitored by the oscillometric method at the time of echocardiographic examination (at least three assessments). All echocardiographic measurements were obtained by the same two observers (R.C. and A.C.), averaging those taken from at least three cardiac cycles.

The evaluation of cardiac performance consisted of the following three analyses:

(1) *Analysis of LV volume, mass, cardiac index and systemic vascular resistance:* According to the pediatric cardiac literature [14], we used the Teichholz formula to calculate from the M-mode LV end-diastolic and end-systolic diameters, septum and posterior wall thickness the following parameters: LV end-diastolic (EDVi) and end-systolic (ESVi) volume index (absolute value indexed to the m^2), ejection fraction (EF% = EDVi – ESVi/EDVi) [15], LV mass index (Mi) and mass/volume (M/V) ratio [16]. Cardiac index (Ci = cardiac output indexed to the m^2), was obtained from the LV volumes multiplied by the heart rate (EDVi – ESVi × HR). Systemic vascular resistance (SVR) was calculated as the ratio between mean blood pressure (BP) and Ci.

(2) *Analysis of LV systolic function, afterload and contractile state:* The parameters obtained from the M-mode parasternal short axis cut of the left ventricle were used to calculate: (a) % fractional shortening (FS); (b) mean velocity of circumferential shortening of the fibers, corrected by HR (mVCFc) [17, 18]; (c) end-systolic meridional stress (ESSm) [19, 20], index of afterload (e.g. the resistance against which blood is expelled at the end of the systole), with end-systolic pressure estimated from the peak systolic and diastolic BP using a regression equation [21] (this method was validated by using invasive measurements), and (d) stress-velocity index (SVI), a parameter of LV contractile state, using the method of Colan [22].

(3) *Analysis of LV diastolic function:* The diastolic function, i.e. the capacity of the left ventricle to accommodate the pulmonary venous return, was evaluated by measuring the Doppler spectral tracing at the mitral inflow: the peak E (first Doppler wave) (E), peak A (second Doppler wave) (A) velocities, the ratio E/A, the deceleration time (DT) (measured as the time interval from the peak E to its extrapolation to the zero line) and the total area under the velocity curve (FVI) were obtained [23]. The ratio E/FVI (recently proposed as index of LV diastolic function, not dependent on HR and preload) was calculated [24]. The isovolumetric relaxation time (IVRT) was measured by CW-Doppler as the time interval between aortic valve closure and mitral valve opening. The following parameters were obtained from PW-Doppler sampling of the pulmonary vein [25]: peak velocity during systole (S) and diastole (D), their ratio (S/D), as well as peak reverse flow (R), corresponding to atrial contraction.

Statistical Analysis

Data are normally distributed and are expressed as mean values ± SD. One-way analysis of variance (ANOVA) with the Bonferroni correction was used to verify differences between patients and controls. A p value < 0.05 was considered statistically significant.

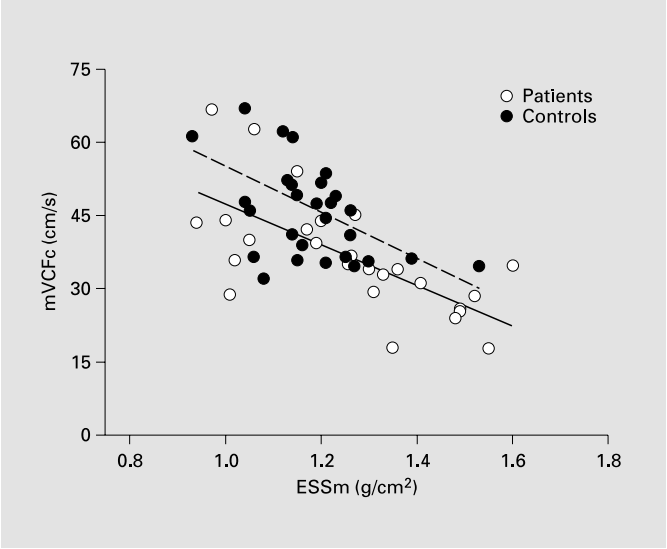

Fig. 1. Relationship between mean velocity of circumferential shortening corrected for HR (mVCFc) and end-systolic meridional stress (ESSm) in patients (○) and controls (●).

Table 2. LV volume, mass, cardiac index and systemic vascular resistance of patients and controls (mean ± SD)

	Patients	Controls	p
EDVi, ml/m^2	61.7 ± 12.2	65.6 ± 10.3	NS
ESVi, ml/m^2	17.6 ± 5.5	20.5 ± 4.0	<0.05
EF, %	71.4 ± 6.8	68.6 ± 4.7	NS
Mi, g/m^2	60.4 ± 9.3	65.3 ± 12.5	NS
M/V, g/ml	1.01 ± 0.25	1.00 ± 0.18	NS
Ci, l/m/m^2	4.01 ± 0.95	3.74 ± 1.01	NS
SVR, dyn·s·cm^{-5}	1,349 ± 369	1,558 ± 404	<0.05

EDVi = End-diastolic volume index; ESVi = end-systolic volume index; EF = ejection fraction; Mi = mass index; M/V = mass/volume ratio; Ci = cardiac index; SVR = systemic vascular resistance.

Table 3. LV systolic function, afterload and contractility of patients and controls (mean ± SD)

	Patients	Controls	p
FS, %	40.6 ± 5.5	38.2 ± 3.6	<0.05
mVCFc, circ/s	1.25 ± 0.19	1.18 ± 0.11	<0.05
ESSm, g/cm^2	36.7 ± 11.9	46.3 ± 9.3	<0.05
SVI	–0.08 ± 1.32	–0.17 ± 0.81	NS

FS = Fractional shortening; mVCFc = mean velocity of circumferential shortening corrected for heart rate; ESSm = end-systolic meridional stress; SVI = stress velocity index.

Table 4. LV diastolic function assessed from the mitral valve inflow of patients and controls (mean ± SD)

	Patients	Controls	p
Peak E, cm/s	91.5 ± 14.7	87.9 ± 14.6	NS
Peak A, cm/s	56.9 ± 11.2	46.1 ± 14.7	<0.05
E/A	1.65 ± 0.37	2.11 ± 0.86	<0.05
DT, s	0.117 ± 0.025	0.138 ± 0.021	<0.05
Peak E/FVI	5.9 ± 0.8	5.5 ± 0.9	NS
IVRT, s	0.055 ± 0.013	0.069 ± 0.007	<0.05

Peak E = peak E velocity; peak A = peak A velocity; DT = deceleration time; FVI = flow velocity integral; IVRT = isovolumetric relaxation time.

Results

HR ($p < 0.002$) and systolic BP ($p < 0.005$) were higher in patients than in controls while diastolic BP was significantly lower ($p < 0.05$); mean BP was similar (table 1).

(1) *Analysis of LV volume, mass, cardiac index and systemic vascular resistance (SVR)* (table 2): LV end-diastolic volume index (EDVi) did not differ but end-systolic volume index (ESVi) was significantly smaller ($p < 0.05$) in patients compared with controls, with no difference in ejection fraction (EF%). Mass index and M/V ratio were not different from controls. The cardiac index (Ci), which represents the cardiac output, was also similar in patients and controls. On the contrary, SVRs were slightly but significantly decreased in patients ($p < 0.05$).

(2) *Analysis of LV systolic function, afterload and contractile state* (table 3): Fractional shortening (FS%) and mean velocity of circumferential shortening (mVCFc) were significantly increased ($p < 0.05$), while end-systolic meridional stress (ESSm) was decreased ($p < 0.001$) in patients vs. controls. Contractile state (SVI) was similar in the two groups. The regression lines between mVCFc and ESSm in TS and controls are reported in figure 1.

(3) *Analysis of LV diastolic function* (table 4): Patients showed a shortening of deceleration time (DT) and of isovolumetric relaxation time (IVRT), with an increased atrial contribution to ventricular filling (peak A, E/A). There was no major derangement of the pulmonary venous flow (table 5).

Table 5. LV diastolic function assessed from pulmonary venous flow of patients and controls (mean ± SD)

	Patients	Controls	p
S, cm/s	43.7 ± 8.8	42.6 ± 8.5	NS
D, cm/s	56.8 ± 15.0	62.1 ± 5.5	NS
R, cm/s	20.4 ± 4.0	18.1 ± 2.4	NS
S/D	0.81 ± 0.23	0.69 ± 0.16	<0.05

S = Peak systolic velocity; D = peak diastolic velocity; R = end-diastolic reversed velocity.

Discussion

The aim of our study was to verify whether long-term treatment of TS patients with high doses of GH could be associated with morphofunctional cardiac alterations, as seen in other situations of GH excess [4, 5]. Clinical evidence suggests that GH plays a major role in inducing acromegalic cardiomyopathy [26] and this view is also supported by in vitro studies. In fact, it has been shown that the gene for GH receptor is expressed at high level in the heart [27], that GH induces increased expression of cardiac insulin-like growth factor-I (IGF-I) messenger ribonucleic acid [28] and, finally, that in vitro IGF-I causes rat cardiomyocyte hypertrophy with increased expression of muscle-specific genes [29]. For this reason we look in our patients for echocardiographic modifications suggestive of ventricular hypertrophy. Our findings are, however, reassuring, since after a mean treatment period of 4.9 years we did not observe any significant alteration in the volume and mass of the left ventricle in TS patients, when compared with a group of girls with constitutional growth delay but similar body surface, in agreement with previous reports [7–9]. Furthermore, the changes we observed in the systolic and diastolic function, but without any anatomical alteration (i.e. ventricular hypertrophy), should not be considered a direct effect of GH, but, more likely, an adaptation to the enhanced HR and reduced peripheral vascular resistance induced by GH. Treatment with GH has been shown in fact to increase HR when administered to normal subjects [30] and to reduce diastolic BP in GHD patients by reducing peripheral vascular resistance [31]. The mechanism behind the reduction of peripheral vascular resistance might be indirect, through reduced obesity and increased insulin sensitivity [32], or more direct, through the action of IGF-I on the vascular wall [33].

Nevertheless, the reduced diastolic BP and SVR may explain the reduced afterload (ESSm) and the increase of the systolic pump function indexes (FS%, mVCFc) with a normal contractile state. The fact that the cardiac index (i.e. the cardiac output indexed at m^2) was normal suggests that our findings do not describe a cardiac hyperkinetic status induced by GH but only an adaptation to a favorable load condition represented by a reduction of the peripheral vascular resistance and of the diastolic pressure. On the contrary, the hyperkinetic status which is seen in the early phase of the acromegalic cardiomyopathy is characterized by reduced vascular resistance, increased HR, increased cardiac output and increased contractile state [26].

The slight alterations of the LV diastolic filling, such as the decrease of the deceleration time and of the isovolumetric relaxation time, may be explained by the increased HR, which could also explain the relative increase of the late filling parameters in PW-D sampling of the mitral inflow. The normal pattern of the pulmonary venous flow is also in agreement with a normal systolic and diastolic function of the left ventricle.

Systolic BP was higher, although still in the normal range, in TS patients. The cause for this finding cannot be explained from our data, however, high BP has been reported in TS [9, 34, 35].

The results of the present study are different from those obtained in our recent survey where the cardiac morphology and function were investigated, with the same modalities, in a group of GHD children treated with the same dosage of GH (1 U/kg/ week) and for a comparable period of time [6]. In that study we showed that the patients had an increase in mass and mass/volume ratio, reduced systolic performance and initial alterations of the diastolic function of the left ventricle after long-term therapy. An explanation for these different findings might be the decreased sensitivity of TS patients to IGF-I [36, 37], which may thus somehow protect them from the high GH serum levels induced by treatment.

In conclusion, our results are reassuring and suggest that TS patients can be treated with high doses of GH for a long period of time without any untoward cardiac effects. A long-term follow-up is however needed to verify whether a longer period of GH treatment would have any undesirable cardiac effects, especially considering that girls with TS do have a higher risk of developing cardiological problems later on in life.

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